Determine the strength of soft bonds

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Abstract

The strength of a simple soft bond under constant loading rate is studied theoretically. We find a scaling regime where rebinding is negligible and the rupture force of the bond scales as $const. + (\ln(kv))^{2/3}$, where kv is the loading rate. The scaling regime is smaller for weaker bonds and broader for stronger bonds. For loading rate beyond the upper limit of the scaling regime, bond rupture is deterministic and thermal effects are negligible. For loading rate below the lower limit of the scaling regime, contribution from rebinding becomes important, and there is no simple scaling relation between rupture force and loading rate. When we extend the theory to include the effect of rebinding we find good agreement between theory and simulation even below the scaling regime.

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Non-covalent molecular bonds in biological systems are soft. Typical binding energy is on the order of $10k_BT$. This extremely weak binding energy enables fast response to external stimuli which is preferred by living systems. [1] At the same time, these weak bonds are sensitive to thermal fluctuations, thus the study of the mechanical response of the bonds has to consider thermal effects. Experimentally, the strength of a soft bond is often characterized by the relation between the rupture force and loading rate, i.e., the dynamic force spectroscopy (DFS). [2] The imposed loading rate in an experiment provides a time scale that can be used to probe the internal dynamics of the bond under study. Therefore DFS experiments of soft bonds have revealed valuable structural and dynamical information for biological soft materials ranging from the energy landscape of several non-covalent bonds to the unfolding mechanisms of several types of proteins [2].

The theoretical problem of finding the rupture force of a bond under constant loading rate corresponds to evaluating the escape time of a particle in a time-varying one-dimensional potential well in the presence of thermal fluctuations. This is an interesting extension of the celebrated Kramers escape theory [3, 4, 5]. To study experimentally relevant problems, extensions of the theory to systems with multiple bonds in parallel [6] or in series [7], and extensions of the theory to bonds which are described by higher dimensional potentials [8, 9] have been studied recently. In the case of multiple bonds, experiments [10] have found good qualitative agreement with theories [6, 7]. In the case of bonds with more than one energy minimum, the theory [9] provides new interpretation for experimental results.

Despite the successes on both experimental and theoretical sides, it is surprising that the conventional "linear theory" [2, 11, 12] for the DFS of a simple one-dimensional bond, the corner stone of theoretical analysis of most experimental studies, is challenged recently by two different theories that we refer to as harmonic theory [6] and cubic theory [13] respectively. Linear theory assumes that under constant loading rate the activation barrier for bond dissociation diminishes linear in time. The resulting rupture force scales like $\ln(kv)$ where kv is the loading rate. Recently, Hummer and Szabo [6] treated the bond as a harmonic potential but ignores rebinding and details of potential shape near the barrier, thus we call this theory harmonic theory. The harmonic theory predicts a relation between the rupture force and the loading rate with the form $const. + (\ln kv)^{1/2}$. At about the same time, Dudko et. al.[13] assumed that bond rupture occurs when the potential energy near the barrier can be approximated by a cubic function, thus we call this theory cubic theory. Cubic theory

follows an earlier work by Garg [4],neglects rebinding, and shows that the rupture force scales like $const. + (\ln kv)^{2/3}$. Ref. [6] showed that the harmonic theory can be extended to describe the unfolding of protein titin, and Ref. [13] showed that the scaling prediction in cubic theory for Morse potential is better than linear theory by comparing the fitting of rupture force in simulation to $(\ln(kv))^{2/3}$ and $\ln(kv)$ respectively. Both Ref. [6] and [13] did not provide a quantitative analysis for the effect of rebinding. In another seemingly unrelated field of the physics of the atomic scale friction, linear theory [14] and cubic theory [15] have both been proposed to describe the rupture of bonds (with no rebinding) between two parallel surfaces under relative motion. Although data from friction experiment [16] is not able to discriminate between linear and cubic theory, it is believed that for atomic friction linear theory works for weak bonds with binding energy slightly greater than $k_B T$ and cubic theory is better for bonds with realistic binding energies which is on the order of $10 k_B T$ [15, 17].

To discriminate between linear, harmonic, and cubic theory, and to provide the underlying physical picture, including rebinding, for the rupture of molecular bonds under constant loading rate, in this Letter we present an analysis of simple bond DFS. Unlike Ref. [6, 13], we do not discuss higher dimensional problems. We focus on simple bonds, we consider loading rate beyond the scaling regime, and we consider the effect of rebinding in our theory. Our result shows that an *extended cubic theory* which takes rebinding into account is suitable to describe the rupture of simple bonds even at low loading rate beyond scaling regime.

In a typical DFS experiment, a bond attached to a surface on one end and a spring on the other end is pulled out by the spring with a constant velocity v until the bond breaks and the spring recoils to its rest position. For a sufficiently simple system, a single reaction coordinate x, usually the distance between the particle and the substrate, is sufficient to describe the dynamics of the system. Let $U_0(x)$ be the potential of the bond and L_0 be its equilibrium position in the absence of external forces. The potential of the spring is $U_{spring}(x,t) = \frac{k}{2}(vt + L_0 - x)^2$ for $t \geq 0$, where k is the spring constant. When the total potential $U(x,t) = U_0(x) + U_{spring}(x,t)$ is bistable, the minimum at smaller x is due to the bond, and it is denoted as $x_a(t)$, the minimum at larger x is due to the spring, and it is denoted as $x_f(t)$, the barrier is denoted as $x_b(t)$. $x_a(t)$, $x_b(t)$, and $x_f(t)$ are determined by solving $-kvt = -(dU_0/dx) - k(x - L_0) \equiv \tilde{F}(x)$. As Figure 1 shows, the solutions to $-kvt = \tilde{F}(x)$ at time t are the crossing points between the stationary curve $y = \tilde{F}(x)$ and the moving horizontal line $y = -kvt$ which scans downward with constant rate kv. Between

t_1 and t_2, $-kvt = \tilde{F}(x)$ has three solutions and $U(x,t)$ is bistable. When $t < t_1$ the bond is stable, when $t > t_2$ the bond is unstable. We further denote the local minimum (maximum) of $\tilde{F}(x)$ as x_1 (x_2),i.e., $-kvt_{1(2)} = \tilde{F}(x_{2(1)})$.

The dynamics of the system along the reaction coordinate is described by the Langevin equation,

$$\frac{dx}{dt} = -\gamma \frac{\partial U(x,t)}{\partial x} + \zeta(t). \tag{1}$$

Here γ is the damping coefficient, ζ is the thermal noise with zero mean and variance $2k_BT\gamma$. For simplicity, we assume γ to be independent of x. The energy unit is chosen to be k_BT, L_0 is unit length, and unit time is chosen such that $\gamma = 1$. When $U(x,t)$ is bistable, the system is in the bound state if $x(t) < x_b(t)$, otherwise it is in the free state. The probability $\phi(t)$ that the system is in the bound state at time t satisfies the reaction equation

$$\frac{\partial \phi(t)}{\partial t} = -k_{off}(t)\phi(t) + k_{on}(t)(1 - \phi(t)), \tag{2}$$

the probability that bond rupture occurs at time t is

$$P_b(t) = \phi(t)k_{off}(t)e^{-\int_t^{t_2} dt' k_{on}(t')} = \left(1 - \int_{t_1}^t dt' k_{off}(t')e^{-\int_{t'}^t (k_{on}(t'')+k_{off}(t''))dt''}\right)k_{off}(t)e^{-\int_t^{t_2} k_{on}(t')dt'} \tag{3}$$

and the mean rupture force is

$$\langle k(vt + L_0 - x_a(t)) \rangle = \int_{t_1}^{t_2} dt P_b(t)k(vt + L_0 - x_a(t)) \tag{4}$$

It is reasonable to assume that time scales to reach local equilibrium in both bound and free states are much smaller than time scales of transitions between the two states. Thus Kramers escape theory [3, 5] states that the on- and off-rates satisfy

$$k(t) = \frac{1}{2\pi}\sqrt{U''(x_\alpha,t)|U''(x_b,t)|}e^{-(U(x_b)-U(x_\alpha))}, \tag{5}$$

where $U''(x,t) = \partial^2 U(x,t)/\partial x^2$. For $k(t) = k_{off}(t)$, $x_\alpha = x_a(t)$; for $k(t) = k_{on}$, $x_\alpha = x_f(t)$

Because bond rupture should occur at t closer to t_2 than t_1, from Fig. 1 it is natural to approximate $\tilde{F}(x)$ by a quadratic function near x_1, and by a straight line near $x_f(t)$. The resulting approximation for $\tilde{F}(x)$ is

$$\tilde{F}(x) \approx \begin{cases} \frac{c}{2}(x - x_1)^2 + f_0, & x < x_2 \\ -k(x - L_0), & x > x_2. \end{cases} \tag{6}$$

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Here $c = -\left(\frac{d^3 U_0}{dx^3}\right)_{x=x_1}$, and $f_0 = -\left(\frac{dU_0}{dx}\right)_{x=x_1} - k(x_1 - L_0)$. Eq. (6) corresponds to a potential that is cubic in x near x_1, and is the spring potential near $x = L_0 + vt$. That is, cubic theory [13], not linear or harmonic theory, follows naturally from observing the generic shape of $\tilde{F}(x)$. A straightforward calculation leads to Kramers on- and off-rates in the cubic theory.

$$k_{on}(t) = \frac{1}{2\pi}\sqrt{k\left(2c(-f_0 - kvt)\right)^{1/2}}\exp\left\{-\frac{c}{3}\left(\frac{2}{c}(-f_0 - kvt)\right)^{2/3} - \frac{k}{2}(x_1 - L_0 - vt)^2 - U_0(x_1)\right\},$$

$$k_{off}(t) = \frac{1}{2\pi}\sqrt{2c(-f_0 - kvt)}\exp\left\{-\frac{2c}{3}\left(\frac{2}{c}(-f_0 - kvt)\right)^{2/3}\right\}. \tag{7}$$

At sufficiently large kv rebinding is unlikely and

$$P_b(t) = k_{off}(t) \times \exp\left(\int_{t_1}^{t} k_{off}(t')dt'\right)$$

$$\approx \frac{\sqrt{-2c(f_0 + kvt)}}{2\pi}\exp\left\{-\sqrt{\frac{32}{9c}}(-f_0 - kvt)^{3/2} - \frac{c}{4\pi kv}e^{-\sqrt{\frac{32}{9c}}(-f_0 - kvt)^{3/2}}\right\}, \tag{8}$$

and the rupture force then has the simple form

$$F_{max} = \left(\frac{dU_0}{dx}\right)_{x=x_1} + k\sqrt{\frac{2\left(\sqrt{\frac{9c}{32}}\ln\frac{c}{4\pi kv}\right)^{2/3}}{c} - \left(\sqrt{\frac{9c}{32}}\ln\frac{c}{4\pi kv}\right)^{2/3}}. \tag{9}$$

The second term on the right hand side of Eq. (9) is $k\langle x_1 - x_a(t)\rangle$, in most cases it is negligible, thus cubic theory predicts the scaling relation $F_{max} \sim const. + (\ln(kv))^{2/3}$. This scaling relation has been tested by data collapsing for simulating Morse potential in Ref. [13]. Here we provide direct comparison between simulation and theory for a couple of potentials so that any discrepancy between theory and simulation can be examined critically. Figure 2 compares the rupture force predicted by Eq. (9) and numerical simulations for Morse potential $U_0(x) = W([1 - \exp(-2b(x - L_0)/L_0)]^2 - 1)$ with $b = 1.5$ and a power law potential $U_0(x) = W(\frac{1}{2(x/L_0)^6} - \frac{3}{2(x/L_0)^2})$ which is taken from Ref. [7], the spring constant is chosen to be $k = 0.8$. Our result shows better agreement between Eq. (9) and simulations for stronger bonds and deviation of simulation from cubic theory at high and low loading rates.

The deviation of simulation from Eq. (9) at high loading rate can be understood by noticing that according Eq. (8), the probability that bond rupture occurs between t_1 and t_2 is

$$\int_{t_1}^{t_2} P_b(t)dt \approx 1 - e^{-\frac{c}{4\pi kv}}, \tag{10}$$

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i.e, at high loading rate with $c/4\pi kv \leq 1$, bond rupture is not likely to occur between t_1 and t_2. This is because from t to t_2 $x_a(t)$ moves a distance $x_1 - x_a(t) = \sqrt{2kv(t_2 - t)/c}$, and the displacement of a particle under free diffusion during the same time interval is $x_d(t) = \sqrt{2(t_2 - t)}$, thus $c/4\pi kv \sim (x_d/(x_1 - x_a(t)))^2$ compares free diffusion and the motion of $x_a(t)$ due to the spring. When $c/4\pi kv \geq 1$, i.e., $x_1 - x_a(t) < x_d(t)$, free diffusion near $x_a(t)$ is faster than the motion of $x_a(t)$, therefore the particle senses the barrier and bond rupture is due to barrier crossing, and Kramers theory is appropriate to describe bond rupture. On the other hand, if $x_1 - x_a(t) > x_d$, free diffusion alone cannot catch up the motion of potential minimum, therefore the particle is located near $x_a(t)$ at all time until the barrier vanishes. That is, thermal effect is negligible in this case. The filled symbols in the high v region of Figure 2 shows where $c/4\pi kv > 2$, and that is when Eq. (9) starts to deviate from simulation result.

The deviation of simulation from Eq. (9) at low loading rate is due to the effect of rebinding. When the chance of observing a rebinding event between the mean rupture time $\langle t_r \rangle$ predicted by Eq. (8) and t_2 is not negligible, i.e.,

$$
\begin{aligned}
&\int_{\langle t_r \rangle}^{t_2} k_{on}(t)dt \\
&= \frac{c}{4\pi kv}\left(\frac{8k^2}{c}\right)^{1/4} e^{-U_0(x_1)} \int_{\left(\frac{c}{4\pi kv}\right)^{-1/2}}^{1} dw \left(-\sqrt{\frac{9c}{8}}\ln w\right)^{-1/6} e^{-\frac{1}{2k}\left(\left(-\sqrt{\frac{9c}{8}}\ln w\right)^{2/3} - U_0'(x_1)\right)^2} \\
&\geq \mathcal{O}(1),
\end{aligned}
\tag{11}
$$

rebinding has to be included in calculation for F_{max}. Filled symbols in the low v region of Fig. 3 are where $\int_{\langle t_r \rangle}^{t_2} k_{on}(t)dt \geq 0.1$. For both Morse potential and power law potential, rebinding is important for weaker bonds. The weaker bonds not only have smaller upper limit for applying Kramers rate theory but also have greater lower limit for neglecting rebinding, therefore the deviation of Eq. (9) is more serious for weaker bonds. The rupture force F_{max} in the regime where rebinding is important can be calculated numerically by extending cubic theory to include nonzero k_{on} in Eq. (7) into Eq. (3) and (4). The long dashed lines in Fig. 2 shows prediction of this *extended cubic theory* in regions where rebinding is not negligible. Indeed extended cubic theory provides a good prediction for rupture force in regions where Eq. (9) deviates from simulation result.

It is interesting to notice that at low loading rate, there is still some difference between the rupture force in *extended cubic theory* and simulation. This reveals the limit of theoretical

description for DFS of simple bonds. Figure 3 shows power law potential with $W = 10$, the case where the difference between extended cubic theory and simulation is most significant, and the potential predicted by cubic theory. Since the cubic theory potential is an expansion of $U_0(x)$ near x_1, it does not fit $U_0(x)$ well for x smaller than L_0. Thus *extended cubic theory* does not have high accuracy when bond rupture time t predicted by extended cubic theory has $x_a(t) < L_0$, and that is when

$$F_{max} < U_0'(x_1) - \frac{c}{2}(x_1 - L_0)^2, \tag{12}$$

where F_{max} is calculated from the *extended cubic theory*. The cross marks in Fig. 2 are where $F_{max} = U_0'(x_1) - \frac{c}{2}(x_1 - L_0)^2$, indeed they mark the limiting loading rates for high precision prediction of extended cubic theory. Finally, we note that in analyzing experimental data, the fitting to extended cubic theory uses data both inside and outside the high precision region. Therefore the resulting information like binding energy and k_{on} should be very close to true values. This explains why data fitting in Ref. [13] is so successful for Morse potential. Thus, extended cubic theory, an attempt to mimic the potential landscape of a bond near where bond rupture occurs, not only captures the basic physical picture of bond rupture, but also provides good quantitative result for analyzing experimental data.

In summary, we have studied the DFS of a simple soft bond theoretically. Our analysis shows that rebinding is important at low loading rate, thermal effect is negligible at high loading rate, in the intermediate loading rate the rupture force scales as $const. + (\ln(kv))^{2/3}$. The numerical simulations for a couple of model potentials with typical binding energy show that the prediction of scaling law is better for bonds with stronger binding energy. Rebinding is important at low loading rate, and *extended cubic theory* fixes the deviation between Eq.(9) and simulation. Our study shows that *extended cubic theory* provides the basic physical picture of the rupture of simple soft bonds. It would very interesting to extend the present model to multiple bonds in series and multiple bonds in parallel and compare to the analysis done in previous studies [6, 7], and that is our future direction.

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Figure captions

- Figure 1: The solid curve is $\tilde{F}(x)$. When $t_1 < t < t_2$ there are three solutions to the equation $-(\partial U_0/\partial x) - k(x - L_0) = -kvt$, they correspond to the potential wells and the barrier between them.

- Figure 2: (a). Rupture force for Morse potential $U_0(x) = W([1-\exp(-2b(x-1))]^2-1)$ with $b = 1.5$ from both numerical simulation and Eq. (9). (b). Rupture force for a power law potential $U_0(x) = W(\frac{1}{2x^6} - \frac{3}{2x^2})$ from both numerical simulation and Eq. (9). Simulation result for $W = 45$ are presented as triangles, circles $W = 30$, diamonds $W = 10$. Filled symbols in the high v region are where Kramers rate theory cannot describe bond rupture, filled symbols in the low v region are are where rebinding is important. Thick dashed lines are from *extended cubic theory*, other lines are from Eq. (9). Cross marks are where $F_{max} = U_0'(x_1) - \frac{c}{2}(x_1 - L_0)^2$, i.e., *extended cubic theory* does not predict F_{max} with high precision when v is smallar than the cross marks. There is no cross mark for Morse potential with $W = 45$, in this case cubic theory agrees with simulation with high precision within the range of our simulation.

- Figure 3: Solid line: power law potential with $W = 10$, dashed line: potential predicted by cubic theory. The prediction of *extended cubic theory* is not highly accurate when $x_a(\langle t_r \rangle)$ is located at region where cubic theory does not fit $U_0(x)$ well, i.e., when $x_a(\langle t_r \rangle) < L_0 = 1$.